UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

OFFICE OF PESTICIDE PROGRAMS
REGISTRATION DIVISION (7505P)

January 15, 2013

MEMORANDUM: Companion Animal Study Citations for 2382-ROE

Subject:	Name of Pesticide Product:	EFFITIX™ PLUS TOPICAL SOLUTION FOR DOGS
	EPA Reg. No. /File Symbol:	2382-ROE
	DP Barcode:	DP 407441
	Decision No.:	468313
	Action Code:	R310
	PC Code:	109701 (Permethrin: 44.6%)
		129121 (Fipronil: 6.0%)
		129032 (Pyriproxyfen: 1.8%)

From: Byron T. Backus, Ph.D., Toxicologist
Technical Review Branch
Registration Division (7505P)

Byron T. Backus
Jan-15-2013
T.L. TOXICOLOGY

To: Driss Benmhend/Richard Gebken RM 10
Insecticide Branch
Registration Division (7505P)

Registrant: VIRBAC AH, INC.

FORMULATION FROM LABEL:

Active Ingredient(s):	by wt.
129121 Fipronil	6.0%
109701 Permethrin	44.8%
129032 Pyriproxyfen	1.8%
Other Ingredients:	47.4%
TOTAL	100.0%

ACTION REQUESTED: "Virbac has requested the registration of this fipronil/permethrin/nylar product. I'm requesting an expedited review... This is the Companion Animal Safety study. The minimum size for the dog was not provided on the label..."

COMMENTS AND RECOMMENDATIONS:

1. This package includes a listing of 29 previously submitted companion animal safety studies. Copies of the data matrix, proposed label and other documents are available from Documentum.

2. Virbac has previously registered (EPA Reg. No. 2382-187) a dog spot-on product with a label declaration of 6.01% Fipronil and 44.88% Permethrin as active ingredients. The additional active in 2382-ROE, Pyriproxyfen (or Nylar), has been demonstrated to have a very low toxicity to dogs, as shown in a 52-week capsule feeding study (MRID 42178309, included in the data matrix citations for 2382-ROE). The companion animal safety studies that were conducted on and/or used to support 2382-187 can also be used to support 2382-ROE, and can also be used by the Agency to set dosage levels. The proposed dosage rates for 2382-ROE are the same as those given on the last accepted (August 28, 2012) label for 2382-187.

3. In a TRB review dated October 13, 2011 it was concluded that in a study in adult beagles (MRID 48467117) the margin of safety in 10- to 20-kg adult beagle dogs administered 104.05 [End-use Product: Effitix™ Topical Solution for Dogs] is at least 5x the recommended dose (2.0 mL/dog). This companion animal safety study in dogs was classified as **Acceptable/Guideline.**

   However, there were two companion animal safety studies (MRIDs 48467118 and 48487302) with 8 week old beagle puppies in which severe adverse effects were seen at the 5X level (5.0 mL/puppy). Both of these studies were classified as **Unacceptable/Guideline because an adequate margin of safety was not demonstrated.** However, no adverse effects were observed at the 3X level (3.0 mL/puppy).

4. EPA Reg. 2382-187 was registered for use on dogs 12 weeks of age and older with a minimum dosage rate of 1.0 mL for dogs weighing less than 22.9 lbs. The registrant then proposed a new dosage rate of 0.5 mL for application to puppies to puppies 8 weeks of age or older and small dogs weighing between 4 and 10.9 lbs. This was accepted (because no adverse effects had been observed at the 3.0 mL/puppy dose in MRID 48467118) in a TRB memorandum dated August 13, 2012. The maximum dosage rate of 0.5 mL to a 4-lb dog is equivalent to 0.28 mL/kg.

5. Virbac subsequently submitted a study (MRID 48951001, not included in the list of studies cited by the registrant for 2382-ROE) on 10-week old beagle puppies as 6(a)(2) data. The adverse effects (including uncontrollable seizures which resulted in the euthanasia of one puppy) that occurred demonstrated that a dosage rate of 1.0 mL/puppy has a less than adequate (5X) margin of safety. The puppy that was euthanized was a male weighing 4.08 kg that received 5.0 mL, equivalent to 1.23 mL/kg; which when divided by 5 gives 0.245 mL/kg. In a review dated December 17, 2012 TRB recommended resetting the minimum weight to 5 lbs (=2.27 kg) which would result in a maximum 1X dosage rate of 0.22 mL/kg.

6. The cited companion animal safety studies adequately support the proposed uses for 2382-ROE, except **the label dosage rates should be revised to specify 5 lbs as the minimum weight rather than 4 lbs.**